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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,527	07/17/2000	AKIKO ITAI	P19291	1282
7055	7590	03/13/2006	EXAMINER	
GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191			KIM, YOUNG J	
			ART UNIT	PAPER NUMBER
			1637	
DATE MAILED: 03/13/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/508,527	ITAI, AKIKO	
	<b>Examiner</b>	<b>Art Unit</b>	
	Young J. Kim	1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 December 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,4 and 6-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,4 and 6-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

The present Office Action is responsive to the Amendment received on December 12, 2005.

#### *Preliminary Remark*

Upon careful reconsideration of the instant application, at least one rejection and/or objection is hereby necessitated, and hence, the present Office Action is made **Non-Final**.

#### *Claim Rejections - 35 USC § 112*

The rejection of claims 1 and 3-10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on June 10, 2005 is withdrawn in view of the Amendment received on December 12, 2005. With respect to the rejection of claims 3 and 5, the rejection is withdrawn due to their cancellation.

#### *Rejection, New Grounds*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, and 6-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites the phrase, "the above scores."

Claim 1 has been amended to include the limitation, "based on the matching score."

Claim 8 recites the limitation, "optimum matching is selected based on calculated scores obtained from environmental information on the side chains of the amino acid residues of the

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reference protein and the hydrophobicity parameters of the corresponding amino acid residues on the query sequence.”

Claim 9 depends from claim 1 and 8. Therefore, it is indefinite to which of the “score,” the limitation “the above scores,” is referring to.

Claim 1 recites that the amino acid sequence of each of the reference proteins is divided in to “two or more core segments,” (see lines 5-6 of the claim), but later recites that wherein amino acid sequence of each of the reference protein is divided into “one or more” core segments. It is confusing how many core segments the reference protein sequence is divided into for the claimed method.

Claims 4 and 6-10 are indefinite by way of their dependency on claim 1.

### ***Claim Rejections - 35 USC § 102***

The rejection of claims 1 and 3-10 under 35 U.S.C. 102(b) as being anticipated by Eisenberg et al. (U.S. Patent No. 5,436,850, issued July 25, 1995), made in the Office Action mailed on June 10, 2005 is withdrawn in view of the Amendment received on December 12, 2005.

The rejection of claims 1, 3-10 under 35 U.S.C. 102(e) as being anticipated by Cohen et al. (U.S. Patent No. 5,878,373, issued March 2, 1999, filed December 6, 1996) made in the Office Action mailed on June 10, 2005 is withdrawn in view of the Amendment received on December 12, 2005.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

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subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 4, and 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenberg et al. (U.S. Patent No. 5,436,850, issued July 25, 1995) in view of SotoJara et al. (U.S. Patent No. 5,948,763, issued September 7, 1999, filed April 10, 1996).

3D-1D analysis is characterized by annotating the environmental information (such as hydrophobicity, hydrophilicity, degree of burial, etc.) of the amino acid residues of a protein of known structure (also called a reference protein) and matching a query protein sequence against the reference sequence, thereby identifying a region of homology, resulting in the prediction that the region of homology in the query protein has the same three dimensional structure to that of the reference protein.

Eisenberg et al. (hereto referred as '850 patent) disclose a method of determining the backbone structure of a query protein of unknown structure by comparing its sequence against a database of reference proteins with known structures and their environmental information (Abstract). The method disclosed by the '850 patent compares an environmental string (or information) of a query protein's residues against the environmental string of the predetermined proteins' residues stored in a database (column 4, lines 25-45; column 6, lines 43-65; column 10, lines 45-65). The method assigns various environmental classes for each residue of the template/query protein, such as buried core structure (hydrophobic) (column 4, lines 53-55), fraction of side chains covered by polar atoms (thus hydrophobic) (column 4, line 55-56), and recites the degrees of burial of the residue (column 4, 57-65). The degree of burial is characterized as buried, partially buried, or exposed (lines 57-58). The '850 patent also generates a 3-D structure profile for each of the environmental string of the proteins, creating a 3D-1D score (column 8, lines

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27-36) and compares the query protein to the predetermined proteins in a database (column 10), resulting in a Z-score which expresses the degree of match (column 11, lines 42-45).

The '850 patent discloses that all sequences in a database of target sequences are aligned with the 3D structure profile using a dynamic programming, which allows insertions and deletions (or gaps) in the alignment (column 10).

The '850 patent does not explicitly disclose that the comparison of the sequences involve segmentation of the reference protein into two or more segments, wherein the segments comprise two or more continuous amino acid residues.

However, Eisenberg et al. (U.S. Patent No. 6,512,981 B1, issued January 28, 2003, priority May 1, 1997) disclose the *inherent property* of dynamic programming algorithm which '850 patent employs:

"The "local" algorithm finds the highest-scoring aligned segment, allowing unpenalized-unaligned N- and C-termini both in the sequence and in the structure. The "global" alignment algorithm allows at most two unaligned termini without penalization, but requires that at least one N-terminus segment and one C-terminus segment of either the sequence or the structure be either aligned or penalized. The preferred embodiment uses a different variation, dubbed the "global-local" alignment. This algorithm does not penalize unmatched N- or C-termini segments in the probe sequence (local alignment), but does penalize any gaps in the target structure (global alignment). This variation produces more reliable scores than those obtained by the commonly used global or local algorithms. See Fischer et al., "Assessing the performance of inverted protein folding methods by means of an extensive benchmark", Proc 1st Pacific Symposium on Biocomputing: 300-318..." (column 9, lines 40-55).

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Since Eisenberg et al. ('850 patent) employs a dynamic programming for the practice of their method, the programming of which involves segmentation analysis of N and C termini segment, and the **inherency** of the dynamic programming disclosed by Eisenberg et al. ('981 patent), the limitation imposed by requiring two or more core segment sequences is clearly met.

While Eisenberg et al. disclose that two or more segment be employed in their method, the artisans do not explicitly disclose that said two or more segments be characterized as a hydrophobic core.

The artisans are also silent with respect to the limitation one or more sub segment sequences which are not predetermined to form a hydrophobic core.

SotoJara et al. disclose the importance of peptide segments found in a protein, said segment comprising a common characteristic of a hydrophobic cluster of hydrophobic amino acids being present within a larger segment strongly predicted to have a  $\beta$ -sheet conformation (column 8, lines 44-49).

The artisans go on to suggest:

“The hydrophobic cluster (or segment) is believed to determine the binding of protein or peptide monomers resulting in aggregation, whereas the longer sequence, of which hydrophobic cluster is a part, is believed to control the ordering of the aggregates into  $\beta$ -cross conformation ( $\beta$ -cross quaternary fibril structure)...” (column 8, lines 49-51)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Eisenberg et al. with that of the SotoJara et al., thereby arriving at the claimed invention for the following reasons.

Eisenberg et al. provides the ground work for characterizing the reference proteins of known 3-D structures, the characterization of which involves identifying, for each of the amino acid residue of each of the reference protein sequence, its hydrophobicity, degree of burial, etc.

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(discussed above). The artisans provide these information obtained from the known 3-D structure of the reference proteins and query a protein of unknown sequence, wherein their sequence homology is compared. Based on the area of homology and the environmental information provided from the amino acid of the reference protein, a structural prediction is made on the query protein.

While the artisans do not explicitly state that the reference protein should be “segmented” into two or more segments which are predicted to form a hydrophobic core, one of ordinary skill in the art would have been motivated to modify the teachings of Eisenberg et al. based on the strong motivation provided by SotoJara et al. who explicitly state that hydrophobic cluster comprising hydrophobic amino acid residues, said hydrophobic cluster comprising “at least three hydrophobic amino acid residues forming [said]... ‘hydrophobic cluster’” (column 8, lines 60-63), control the protein structure (i.e.,  $\beta$ -cross conformation).

One of ordinary skill in the art at the time the invention was made would have been clearly motivated to identify multiple segments on the reference protein (of Eisenberg et al.), said segments comprising hydrophobic residues, so as to facilitate the prediction of the protein folding of a query protein.

One of ordinary skill in the art would have had a reasonable expectation of success at producing the combination as Eisenberg et al. already provides the teaching for characterizing all residues of the reference proteins of known three-dimensional structure. Hence, identifying segments comprising at least 3 hydrophobic residues therefrom and characterizing them as a hydrophobic segment would have been made with a clear expectation of success, thereby rendering the instant claims *prima facie* obvious over the cited references.



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### *Conclusion*

No claims are allowed.

Applicant's arguments with respect to claims 1, 4, and 6-10 have been considered but are moot in view of the new ground(s) of rejection.

In addition, Applicants appear to argue that the term, "core segment," is distinguished from "any segment comprising two or more amino acid residues." (page 11, 1<sup>st</sup> paragraph, Response).

This argument is persuasive to the point that so long as the two or more amino acid residues "participate" in protein folding, such residues make up a core segment. In addition, the specification to which Applicants point to gives only an exemplary definition, not an explicit definition.

### *Inquiries*

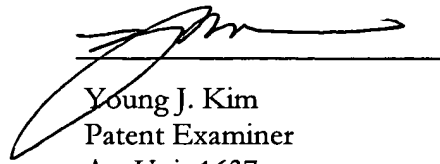
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to [Young.Kim@uspto.gov](mailto:Young.Kim@uspto.gov). However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be

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sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.



Young J. Kim  
Patent Examiner  
Art Unit 1637  
3/9/2006

**YOUNG J. KIM  
PATENT EXAMINER**

yjk